Original Research

Chemicals, birth defects and stillbirths in New Brunswick: associations with agricultural activity

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We describe a series of investigations that were conducted in support of the Task Force on Chemicals in the Environment and Human Reproductive Problems in New Brunswick. Geographic and temporal analyses and case-control studies, with the use of vital statistics, hospital records, the Canadian Congenital Anomalies Surveillance System and chemical databases, revealed no association between pesticides used in forestry and reproductive problems. Evidence of an association between the potential exposure to agricultural chemicals and three major anomalies combined as well as spina bifida without hydrocephalus was found. More plausible was an association between stillbirths and such exposure during the second trimester of pregnancy. This finding, along with the cyclic patterns of stillbirth in the agricultural Saint John River basin and the somewhat higher stillbirth rates in New Brunswick than in adjacent provinces or in Canada as a whole, suggests that further attention should focus on possible associations between agricultural activity and stillbirths.

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Les travaux dont nous faisons état ont été entrepris sous l'égide du Groupe de travail sur les effets des produits chimiques du milieu ambiant sur la reproduction humaine au Nouveau-Brunswick. L'analyse de l'emploi des pesticides dans l'exploitation forestière selon le temps et le lieu ne les met pas en rapport avec les troubles de la reproduction; on a utilisé à cette fin des comparaisons cas-témoin, les statistiques sanitaires, la revue de dossiers hospitaliers, les données du Réseau canadien de surveillance des malformations congénitales, aussi bien que des renseignements chimiques. Mais il existe un rapport entre la possibilité d'exposition aux produits chimiques agricoles vers le temps de la conception et trois malformations congénitales majeures combinées aussi bien que le spina bifida sans hydrocéphalie d'une part, et un rapport plus net avec la mortinatalité pendant le deuxième trimestre d'autre part. Vu l'évolution cyclique de la mortinatalité dans la vallée agricole du Saint-Jean et son plus haut taux au Nouveau-Brunswick que dans les provinces limitrophes et qu'au Canada dans son ensemble, il y a lieu d'étudier plus avant leurs liens possibles avec l'agriculture.

In recent years there has been increased concern about possible health risks from the aerial spraying of forests in New Brunswick each spring to combat the spruce budworm. Dichlorodiphenyltrichloroethane (DDT) was used from 1952, when the program began, to 1967, when DDT's dangers became apparent; since then other chemicals, mainly fenitrothion and aminocarb, have been used. In addition, 2,4-dichlorophenoxy acetic acid (2,4-D) and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) have been aerially sprayed in forests to control plant growth; 2,4-D has also been used for agricultural purposes and for the maintenance of right-of-ways for hydroelectric power lines.

Examination of possible adverse effects of pesticides on human reproduction outcomes has proved to be complex and controversial. Epidemiologic studies have explored the potential health effects, especially reproduction outcomes, of the military's use of herbicides and defoliants during the Vietnam War.[1] Reports from a symposium in Ho Chi Minh City, Vietnam, suggested that exposure to Agent Orange (a herbicide composed of 2,4-D and 2,4,5-T, with dioxin as a contaminant) was associated with a high incidence rate of adverse reproduction outcomes, especially molar pregnancies, among the Vietnamese population.[2,3] Westing[4] added, however, that these data require further assessment with more rigorous methodology. Government-commissioned case-control studies of Australian and American male veterans[5-7] did not reveal any clear patterns of increased reproductive risks among these groups.

Case-control studies have also been conducted in nonmilitary contexts. Gordon and Shy[8] used ecologic data to explore simultaneous maternal exposure to multiple agricultural chemicals in Iowa and Michigan and found an increased risk for facial clefts among offspring. Nelson and colleagues[9] found a similar association in Arkansas but attributed it to better case finding and not to an increased risk. Studies of occupational groups — agricultural sprayers in New Zealand[10] and chemical factory workers in Michigan[11] — did not reveal increased reproductive risks.

Information on the possible effects of maternal exposure to chemicals used in forestry and agriculture is sparse. Indeed, for forestry insecticides there appear to have been no relevant epidemiologic studies. The lack of such information may stem from difficulties in measuring the exposure to these chemicals and in assessing the incidence of adverse reproduction outcomes, which may be quite rare or may not be amenable to accurate reporting (e.g., spontaneous abortion). Policy-makers thus have limited information to assist them in making management and regulatory decisions, and the public has received little guidance from scientists or government officials to help them deal with their health concerns. These deficiencies are compounded by difficulties in accessing pesticide registration data in Canada.[12]

In New Brunswick public concern and media attention have been primarily directed toward possible health effects associated with several decades of insecticide use to combat the spruce budworm. The Task Force on Chemicals in the Environment and Human Reproductive Problems in New Brunswick, an international panel of scientists under the chairmanship of Dr. J. Donald Hatcher, was commissioned by the New Brunswick Department of Health to examine the data on forestry and agricultural chemical use in relation to the indicators of reproductive health for the province, particularly from 1971 to 1981.[13]

The task force initially surveyed the relevant literature and assessed the patterns and trends of reproduction statistics, with particular emphasis on comparisons with the patterns and trends of the adjacent provinces — Quebec and Nova Scotia. The occurrence of birth defects in New Brunswick was compared with that in five other provinces, data for which were available from the Canadian Congenital Anomalies Surveillance System (CCASS), a monitoring system established in 1966 by the Health Protection Branch of the Department of National Health and Welfare.[14] Despite generally lower rates of reported birth defects, the rates of neural tube defects were higher for New Brunswick than for the five other provinces. Counties within the agricultural Saint John River basin had generally higher anomaly rates and more often had unusual seasonal peaks compared with other counties. Spectral analyses of the incidence of stillbirths revealed an approximately annual cyclic pattern in seven adjacent counties, six of which were within the Saint John River basin.[15] These preliminary findings provided the framework for the series of studies described in this report.

Methods

Data collection

Data on reproduction outcomes were obtained from two main sources. Information on stillbirths was provided by Statistics Canada and information on birth defects by the CCASS.

Information on the use of chemicals was assembled in a format compatible with that used for the data on stillbirths and congenital abnormalities. Data on the use of chemicals in forestry were primarily derived from maps and records compiled by the spray application companies and the New Brunswick Department of Environment. The maps are based on prior approval of spray intentions, with regard to chemical composition and areas to be sprayed, and are adjusted for actual applications after spraying. Chemicals are sprayed under specific weather conditions to minimize aerial drift and to maximize accuracy. The incentives for this process have to do with efficacy, economics and accountability and in these respects are considered to be reliable. However, some drift inevitably occurs, and the exact boundaries of maximum spray deposit cannot be strictly defined. Furthermore, we realize that there is a distinction between potential exposure and actual dose received by a person, but validation of exposure estimates was beyond the scope of this study. Such potential errors would be randomly distributed in reference to case and control groups and would dilute possible underlying associations.

Data on the use of chemicals in agriculture were difficult to obtain. There are no records for most of the period in question, and data on crop production (upon which estimates of chemical use could be based) exist only for census years. The task force therefore used maps of soil capability, which grade areas in terms of their suitability for agricultural production, to serve as a basis for an agricultural chemical exposure opportunity (ACEO) index.

Exposure and outcome variables

Seven pesticide categories were considered: fentrothion formulations, aminocarb formulations, other forest insecticides, herbicides with some phenoxy component, herbicides with only phenoxy, chlorinated herbicides and nonchlorinated herbicides. The first three categories were recorded according to mass (kilograms of active ingredient per county), and the remainder were based on area (number of hectares sprayed per county).

The selection of birth defects was based on three general criteria: unusually high prevalence rates, evidence that exposure to certain pesticides might have been a plausible cause and availability of sufficient data from the surveillance system. Three types of abnormalities were identified: neural tube defects,[16] facial clefts[8,17] and bilateral renal agenesis.[18] Most of the cases associated with these abnormalities were thought to be well ascertained by the CCASS, and there was no reason to expect significant variations in New Brunswick during the study period. In addition, a combined category of these birth defects and a combined category of 40 abnormalities documented by the CCASS, as well as stillbirths, were analysed.

Correlation analyses

Because exposure may produce effects over a long period, depending on gestational age and type of outcome, correlation coefficients were calculated between outcome and exposure in all counties over the available period for each of four lag intervals: for the purpose of lagged analyses the year is divided into four quarters. Within each quarter, outcome can be correlated with exposure (a lag 0 analysis). However, if there is a relation, the outcome may be delayed one, two or even three quarters from the time of spraying if the time required for fetal development is considered. In addition, some unknown delay may exist between the time of spraying and certain types of indirect exposure (e.g., to water and food). For these reasons a series of four analyses was carried out for all quarters in the period studied, corresponding with lags 0, 1, 2 and 3. All correlation coefficients were assessed in terms of whether the lag intervals were consistent with recognized periods of fetal organogenesis. The strength of the association between the rate of occurrence of the abnormalities and the degree of exposure to each of the seven chemical groups (at all quarterly lag intervals) in each county when spraying actually took place was measured with the Pearson correlation coefficient.

Comparison of mean rates

The mean rate of occurrence for each outcome of interest when spraying took place and the corresponding mean rate in the subsequent three quarters (and all quarterly lag intervals) were compared for each county-chemical combination. The purpose of this analysis was to assess whether a presumed exposure was followed by an elevation in the rates of outcome and, if so, by what length of time. This analysis complemented the lagged correlation analysis because it included data for counties and quarters in which no spraying took place.

Case-control studies

Cases were those ascertained by the CCASS from 1973 to 1979, the period judged to have the most complete ascertainment of abnormalities. Controls were identified from the Provincial Registry of Livebirths and were selected by Statistics Canada. When more than one eligible control was available, selection was effectively random. Each case-control study contained approximately two controls for every case: one set of controls was matched to the cases for date of birth and sex, and the second set was matched for county and date of birth but was chosen from a different year. The first set of controls, therefore, fully exploited the geographic variability, and the second set exploited the yearly variations, when applicable, in the amount and the areas sprayed. The final numbers of cases and controls were not identical because of the exclusion of a few people who were in New Brunswick at the time of birth but were not provincial residents. Table I describes the sample characteristics of the study.

To estimate the power of the study of stillbirths, the minimum detectable relative risk was calculated by the assumption that there were 295 cases, an equal number of controls and a prevalence rate of exposure of 30% (based on the highest prevalence rate obtained). The relative risks detectable under these circumstances are a function of two probabilities: that the null hypothesis will be rejected when it is actually true (α) and accepted when it is incorrect (β). A minimum detectable relative risk of less than 2.0 can be achieved when α is 0.05 at all three levels of β (0.05, 0.1 and 0.2). This relative risk compares reasonably well with those of many other studies in environmental health and gives some idea of the potential power of this study under these fixed assumptions. The same power calculations apply when the three main defects are combined.

The residence was the municipality where the mother lived at the time she gave birth; an "exposure-risk window", the critical period of organogenesis or fetal development during which a chemical exposure could have a teratogenic effect, was calculated for each person. The first trimester included the 2 weeks before and the 13 weeks after conception, a period of susceptibility to birth defects. The second trimester was from 14 to 27 weeks' gestation. An additional exposure-risk window was established for neural tube defects: a "periconceptional" period, from 2 weeks before to 5 weeks after conception. The following procedure was used to calculate the exposure-risk windows.

- For each case or control subject for which the risk window coincided with a spray period the mother's place of residence was determined and located on the appropriate map.
- A circle with a 5-km radius was centred over the residence on the map. The circle represented an area of approximately 78.5 km^2 and contained 100 dots, each dot being positioned so that it represented 1% of the area.
- Potential exposure to forestry insecticides was quantified by counting the number of dots in the circle that were superimposed on the sprayed areas on the map. If none of the dots were so superimposed, the potential exposure was represented by 0%, whereas if half of the circle was superimposed on a sprayed area the potential exposure was 50%. The ACEO index was determined in a similar manner, the period of agricultural activity during which chemicals are used being considered. Because of the imprecise areas on the map that depicted areas sprayed with phenoxy herbicide, only a plus or minus score was assigned for this group of chemicals.

Because a temporal association was found between insecticide use and stillbirths at the first lag interval (approximately a second-trimester exposure), a set of case-control studies of stillbirths in the second trimester was also conducted. Results of all analyses were stratified by control group, length of gestation, maternal and paternal age, and geographic location (upper or lower New Brunswick counties or the Saint John River basin). Standardized risk ratios (SRRs) were calculated for all exposure categories and assessed for statistical significance.

Confidence limits of 95% were calculated for all SRR estimates and were mostly derived by an iterative method,[19] except in instances involving small numbers.[20] Chi-squared tests for association were performed in all comparisons of exposure to test the null hypothesis that the SRR was 1.0 (i.e., there was no effect of that level of exposure on the outcome). In addition, chi-squared tests for homogeneity to test the null hypothesis that all of the SRRs were 1.0 simultaneously and for trend in disease risk with increasing levels of exposure were carried out in accordance with methods described by Armitage;[21,22] these two approaches correspond with "all-or-none" and "dose-response-gradient" hypotheses of biologic responses to exposure. Summary analyses, adjusted for the strata noted previously, were carried out with the use of the Mantel-Haenszel method.[23] The level that was set for statistical significance in any instance was $\alpha = 0.05$.

Limitations

For statistical analysis it was necessary to group formulations without reference to additives or emulsifiers, and no account could be taken of variation in the concentrations of impurities.

Table I — Number of cases and controls in studies of birth defects and stillbirths possibly associated with pesticides and herbicides in New Brunswick

Birth defects/ stillbirths*	No. of cases	No. of controls†	
		Group 1	Group 2
Neural tube defect (NTD)‡			
Anencephaly	103		
Spina bifida			
With hydrocephalus	58		
Without hydrocephalus	74		
Cleft palate	47	384	386
Cleft lip			
Alone	39		
With cleft palate	41		
Renal agenesis	30		
Stillbirth	298	299	302

*The numbers of stillbirths and controls were not exactly equal because of the exclusion from the study of some women from other provinces.
†The same controls (both groups) were used in all case–control analyses of birth defect categories.
‡The subcategories of NTD are not mutually exclusive, as 11 cases had two subcategories of defect, always anencephaly and another NTD subcategory.

Spray-intention records were adjusted for actual application, but the potential for errors in estimating or recording could not be assessed. The data available did not permit adjustment for personal geographic mobility on a daily or multiple residential–work station basis, so that each subject had to be viewed as an "average", based on a fixed location. Some people also may have changed their residential address between the time of potential critical exposure (the exposure window) and the time they gave birth, when the residential address was recorded. Although aerial drift occurs because of fluctuations in temperature, humidity, wind velocity and spray technology, it was not feasible to take these factors into account. In addition, exposure and dose were not synonymous, and no account was taken of the type of employment, which could have involved occupational exposures.

The correlation analyses and comparisons of mean rates were conducted only as exploratory ecologic studies, which might none the less reveal associations worthy of further investigation. The case–control studies, which were based on individual estimates of potential exposure, offered the most acceptable basis for judging the presence or absence of an association.

For the study of birth outcomes a short-term exposure–outcome model was considered most plausible. However, the possibility of long-term cumulative effects cannot be ruled out, although such effects were considered less likely on the basis of current knowledge. Similarly, our studies focused on maternal exposures; paternal exposures might also have been of some importance, but there is less precedent.

Despite these limitations, the exposure information for chemicals used in forestry compares favourably with the information on environmental health issues in general and is far superior to that available on the use of the chemicals in agriculture. Lack of data on agricultural use led to the development of the ACEO index, which indicated potential exposure but not necessarily actual chemical use or exposure.

Results

Correlations and comparisons of mean rates

Because of the data limitations just described, these preliminary analyses could be conducted only for forestry pesticides. Correlation analyses of discrete anomaly categories and subcategories revealed 19 statistically significant positive coefficients, when approximately 14 had been expected by chance; only 10 corresponded with embryologically plausible lag intervals after exposure: 5 were associated with exposure to insecticides and 5 to herbicides. The strength of the correlation coefficients was adequate for further study in four instances of insecticide use and in two of herbicide use. None of the coefficients gained further support from the comparison of the mean birth defect rates between sprayed and unsprayed periods at the appropriate lag interval. Given the inconsistency between the results of the correlation analyses and comparisons of mean rates, these findings could have little importance.

Case–control studies

No overall association was detected between the number of stillbirths and potential exposure to fenitrothion, aminocarb, phenoxy herbicides or agricultural chemicals during the first trimester of pregnancy. The highest estimated relative risk was found for the gestational age of 20 to 29 weeks in relation to the ACEO index, but this was not statistically significant.

The combined category of all neural tube defects, facial clefts and renal agenesis was not associated with potential exposure to insecticides and herbicides used in forestry, phenoxy herbicides or chemicals used in agriculture. However, in the analyses of geographic location (upper or lower New Brunswick counties) the two significantly elevated SRRs were at the highest level of postulated exposure to agricultural chemicals in the upper counties (Table II).

Table II — Standardized risk ratios (SRRs) for a severe congenital anomaly after potential exposure to agricultural chemicals 2 weeks before and 5 weeks after conception, by control group and residence in upper and lower regions of New Brunswick

Control group; region	Not in exposure window	Agricultural chemical exposure opportunity index category; SRR			
		0*	1–10	11–40	≥ 41
Group 1	1.00				
Upper		†	0.86	0.65	2.49‡
Lower		1.26	1.99	1.94	1.08
Group 2	1.00				
Upper		3.13	1.63	0.80	1.97‡
Lower		0.98	3.72	1.13	1.07

*In exposure window but zero exposure.
†Insufficient data for calculation of risk ratio.
‡$p < 0.05$.

None of the facial cleft categories (cleft lip and palate, cleft lip alone and cleft palate alone) nor anencephaly was associated with potential exposure to fenitrothion or agricultural chemicals during the first trimester of pregnancy. There was also no association between anencephaly and such an exposure during the periconceptional period.

There was some evidence that all neural tube defect categories combined were associated with potential exposure to agricultural chemicals during the periconceptional period. Examination of the subcategories revealed a fairly strong association between spina bifida without hydrocephalus and the ACEO index (p = 0.01) (Fig. 1). This association was characterized by substantially elevated estimated risks in the upper counties and the Saint John River basin. Analysis of the combined category of all spina bifida defects failed to reveal any relation to the ACEO index during the periconceptional period.

The case-control studies of renal agenesis were limited because of the small sample (only 30 cases). Although no clear evidence of an association was obtained between this group and potential exposure to fenitrothion or agricultural chemicals, the possibility of an association with fenitrothion was raised because of a statistically significant elevation of the SRR in the lower of two categories of exposure during the periconceptional period in reference to the first control group. This may warrant further consideration.

Stillbirths were found to be significantly associated with potential exposure to agricultural chemicals during the second trimester and showed some evidence of an exposure-response gradient (p = 0.0332) (Fig. 2).

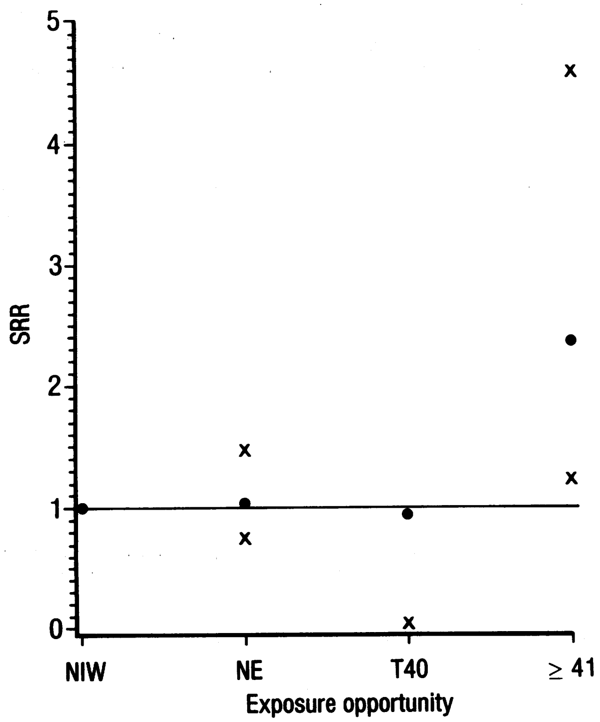

Fig. 1 — Standardized risk ratios (SRRs) for spina bifida without hydrocephalus after potential exposure to agricultural chemicals during periconceptional period, adjusted for residence in Saint John River basin. NIW = not in exposure window; NE = in exposure window but no exposure; T40 = exposure opportunity index categories 1 to 40; upper limit on T40 is 114.1. × represents 95% confidence limit; χ^2 linear trend p value = 0.01.

Discussion

The nature of this investigation, in the context of public concern, required that any possible association between the exposures and the outcomes selected for the study had to be examined. This inevitably meant that many statistical tests had to be performed, and there was a consequent risk of multiple-testing bias. However, statistical significance was not the sole criterion of association.

In assessing the results of these studies, we considered evidence of an association acceptable if it stemmed from a case-control study and consisted of statistically significant differences or trends in risk across ordered categories of exposure, in a direction consistent with an exposure-response gradient, during an embryologically plausible exposure period. Other criteria included the specificity and strength of the association, the consistency with other epidemiologic evidence in New Brunswick, and the existence of compatible experimental and epidemiologic evidence from the scientific literature. These criteria are in accordance with

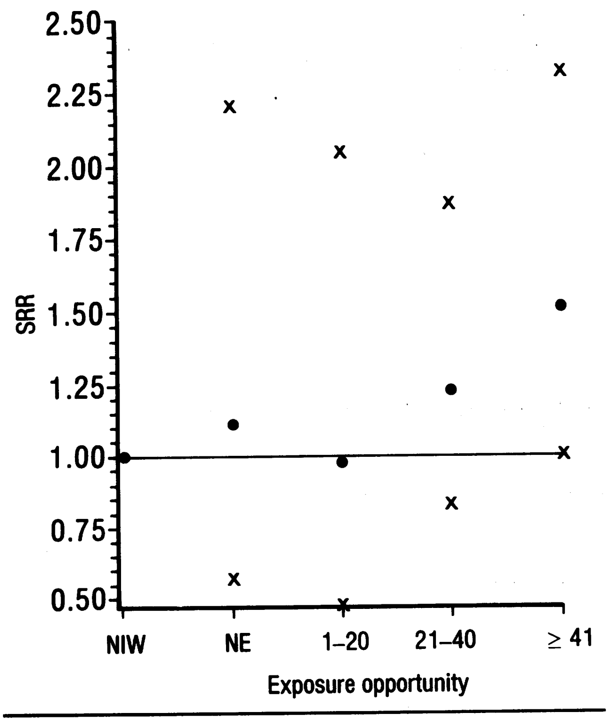

Fig. 2 — SRRs for stillbirth after potential exposure to agricultural chemicals during second trimester, adjusted for maternal age. Mantel–Haenszel extension p value = 0.0332.

those described by Hill[24] in 1965, which are now widely applied to the problem of causal inference. Elevated correlation coefficients or differences in the mean rates of outcome between exposure and nonexposure periods that were not supported by findings from a case-control study were not accepted as evidence of association.

No acceptable evidence of an association was thus found between any of the forestry pesticides studied and any outcome category, except perhaps for fenitrothion in the first trimester and renal agenesis. Although not supported by correlation analysis and comparisons between mean rates, an underlying association might not have been detected because of the small numbers. There was insufficient evidence of a causal association, and even the existence of a noncausal association should be seriously questioned.

An association between the ACEO index and the combined category of the three main defects was considered biologically plausible because of compatible experimental and epidemiologic evidence, even though this association lacked good evidence of a biologic gradient, strength and specificity. The fact that spina bifida without hydrocephalus and not the combined category of all spina bifida defects was associated with the ACEO index detracted from the plausibility of this association. The ACEO index, although based on our extrapolation from land use and recommended chemical use, might none the less represent some nonchemical characteristic (e.g., work patterns related to agricultural land use). The case of underlying causes clearly must be further investigated in the region, given the importance of neural tube defects.

The association of stillbirths and exposure to agricultural chemicals during the second trimester of pregnancy showed some evidence of an exposure–response gradient but could not be considered specific because neither the ACEO index nor the stillbirth rate was a discrete entity. Consistency is gained from the previous evidence of cyclic patterns of stillbirths within the Saint John River basin and the somewhat higher stillbirth rates in New Brunswick than in Quebec and Nova Scotia or in Canada as a whole. This association must be explored further.

Recent studies of nitrate levels in Carleton County, conducted by the New Brunswick Department of Health, have revealed elevated levels in up to 18% of the wells sampled (Donald J. Ecobichon et al: unpublished data, 1985). Although there was some evidence of seasonal fluctuation in the nitrate concentrations, the variation rarely exceeded 30%. An Australian study of maternal drinking water and birth defects revealed an association between nitrate concentrations and the risk of neural tube defects.[25] A groundwater contamination hypothesis may be compatible with our ACEO index association, which includes a seasonal as well as a land-use component.

We realize that there were methodologic limitations to our study. In addition to the assumptions underlying estimated exposures and the limited statistical power to identify rare associations, it is possible that some women who knew they were exposed to chemicals had therapeutic abortions. Such limitations would tend to dilute any underlying associations and therefore strengthen the argument for further investigation in light of the actual findings, particularly in the agricultural context.

The results we have presented suggest that further attention be focused on the possible associations between factors in the agricultural environment and reproduction problems, particularly neural tube defects and stillbirths. This suggestion is reasonable because of the increased potential for hazardous exposures in agricultural areas: chemicals are applied close to dwellings, and farmers, along with their helpers and families, may have minimal training in handling, applying and disposing of chemicals. Chemicals or their residues may be brought into the home on clothing and food and may contaminate water supplies. Future research should also consider nonchemical hazards such as physical or emotional stress and mechanical accidents.

We gratefully acknowledge the support of the New Brunswick Department of Health as well as the technical assistance of the Department of National Health and Welfare, Statistics Canada and Hugh Millward, Department of Geography, Saint Mary's University, Halifax.

Members of the Task Force on Chemicals in the Environment and Human Reproductive Problems in New Brunswick were Dr. J. Donald Hatcher (chairman), Dalhousie University, Halifax; Dr. Franklin M.M. White (vice-chairman), Dalhousie University; Dr. Irvin Emanuel, University of Washington, Seattle; Dr. Jacqueline Fabia, Laval University, Quebec; Dr. F. Clarke Fraser, Memorial University, St. John's; Dr. Gerald S. Marks, Queen's University, Kingston, Ont.; Dr. Ross McCurdy, Dalhousie University; Dr. Victor D. McLaughlin, Saint John, NB; Dr. Godfrey P. Oakley, Centers for Disease Control, Atlanta; Dr. Jack Siemiatycki, Institut Armand Frappier, Montreal; Dr. Elizabeth Winsor, Dalhousie University; Dr. Fay G. Cohen (research officer), Dalhousie University; and Dr. Greg Sherman (consultant), Department of National Health and Welfare, Ottawa.

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